

REMARKS

New claims 18-37 have been added. New claim 18 relates to compositions that comprise an extruded component prepared using the process of Claim 1; wherein said composition comprises one or more active ingredients that are not sulfonamide herbicides (see page 25, lines 6-8). New Claim 19 generally corresponds to Claim 10 except that in Claim 19 metsulfuron methyl is not included in the sulfonamide herbicide free acid listing. New claims 20-30 generally correspond to claims 2-9 and 15-17, except that the new claims depend directly or indirectly from Claim 19 instead of Claim 1. New Claim 31 lists certain inorganic bases (see page 6, line 32; but Claim 31 does not include sodium carbonate). New Claim 32 generally corresponds to Claim 9 except that Claim 35 recites disaccharide rather than saccharide (see page 28, lines 10-11). New claims 33-35 generally correspond to claims 12-14, except that the new claims depend directly or indirectly from Claim 32 instead of Claim 1. New Claim 36 relates to embodiments wherein the mixture comprises two or more active ingredients (see page 25, line 6-8). New claim 37 is a composition claim with a sulfonamide herbicide free acid recitation as in process Claim 19.

I.

In the Office Action, claims 1-3, 9-11 and 15-17 were rejected under 35 U.S.C. 112, first paragraph as failing to comply with the written description requirement. The Office Action noted that the specification discloses some common bases suitable for the invention, that the examples of certain sulfonamide compositions are provided. Nevertheless, the Office Action maintained that the description must convey what the compound is, not just what it does (*University of Rochester v. G.D. Searle & Co.*, 69 USPQ2d 1886, 1895 (Fed. Cir. 2004) was cited); the language of the claims specification does not reasonably provide enablement for inorganic base equivalents having conjugate pK_a s at least 2.1 greater than the highest pK_a of the sulfonamide free acid component; and that the instant specification fails to provide guidance that would allow the skilled artisan to practice the invention without resorting to undue experimentation (*In re Wands*, 8 USPQ2d 1400, 1404 (CAFC 1988) was cited).

Applicants submit that the *University of Rochester* case involved a situation where “[n]o compounds that will perform the claimed method are disclosed, nor has any evidence been shown that such a compound was known” (see 69 USPQ2d at 1895). Applicants note that the *University of Rochester* case contrasted that situation to several others including the situation in *In re Herschler* 200 USPQ 711 (CCPA 1979) where adequate written description was found to support broad claims to processes for topically administering a physiologically active steroidal agent to a human or animal by concurrently administering the steroidal agent and dimethyl sulfoxide, even though the specification disclosed only one example of a physiologically active steroidal agent (see 69 USPQ2d at 1896). It was noted that in the *In re*

Herschler situation there was no question that numerous physiologically active steroidal agents were known to those of ordinary skill in the art (see 69 USPQ2d at 1896). Accordingly, Applicants submit that the University of Rochester case raises description concerns where there no known examples that meet a claim limitation; and not where examples that meet the claim limitation are clearly known. Applicants note that in the present application, numerous inorganic bases are disclosed in the specification; and Applicants submit that there is no question that numerous inorganic bases are known to those of ordinary skill in the art. Indeed, Applicants note that the use of “base” in patent claims is readily apparent (see e.g., U.S. Patent 7,192,906 – Claim 2; U.S. Patent 7,230,116 – Claim 7; U.S. Patent 7,268,259 – Claim 3; and U.S. Patent 7,285,678 – Claim 1).

With regard to pK_a , Applicants submit that pK_a is very well known to one of ordinary skill as a principal measure for describing the acidity of acids, and basicity of bases (in terms of pK_a of their conjugate acids). As an introduction to this concept, Applicants are providing along with this Amendment a copy of section IX “ACIDS AND BASES” from A. J. Gordon and R. A. Ford, *The Chemist’s Companion*, Wiley-Interscience, New York, 1972, pp. 54–80. As noted in the Office Action, Table B of the present application lists, as a convenience to the reader, pK_a values relevant to seventeen of the most common bases. Applicant submits that there is an enormous amount of published data on the topic of pK_a ; and that, as is stated in the last paragraph on page 57 of the excerpt of the book provided, it is impractical to include an exhaustive collection of acidity data even in a book such as *The Chemist’s Companion*. Nevertheless, Applicants submit that pK_a data for numerous inorganic bases is known, and as recognized in the Office Action, pK_a s can be readily determined using standard methods.

Applicants note the attempt in the Office Action to apply an “eight Factor” test for assessing whether undue experimentation is required, and do not agree with the assessment in the Office Action. For example, Applicants note certain comments in the Office Action regarding “bioavailability” and submit that the Office Action provides no basis for asserting that “bioavailability” based on structure is pertinent as a factor which needs to be addressed for enablement of the claimed invention. Moreover, Applicants note that no assessment of “factor 6” appears to have even been attempted. In any event, Applicants submit that this is not an instance where a complex analysis needs to be made to determine whether undue experimentation is required. Applicants have disclosed that including certain amounts of an appropriate inorganic base in the recited mixture for extrusion pursuant to the claimed process is advantageous. One need only determine the pK_a s of the sulfonamide herbicide free acid component and of the conjugate acid of the inorganic base under consideration; and if the pK_a of the conjugate acid has pK_a at least 2.1 units greater than the highest pK_a of the

sulfonamide free acid component the base is an appropriate one. The pK_a s pertinent to numerous sulfonamide herbicides and inorganic bases are known and many are even listed in the specification. As recognized in the Office Action, pK_a s can be readily determined using standard methods. Enablement is not precluded by the necessity for some experimentation such as routine screening (see *In re Wands*, 8 USPQ2d at 1404). Accordingly, Applicants submit that routine screening such as standard pK_a determinations should clearly not be considered undue experimentation.

In sum Applicants submit that the claimed invention is sufficiently described and enabled.

II.

In the Office Action, claims 1-3, 9-11 and 15-17 were rejected under 35 U.S.C. 112, second paragraph as being indefinite. The Office Action suggested that one of ordinary skill in the art would not know how to determine what is meant by the term “at least about 50 equivalent % (and 75 equivalent % or 100 equivalent %) of base selected from inorganic base equivalents having conjugate pK_a s at least about 2.1 units greater than the highest pK_a of the sulfonamide herbicide free acid component”; and that units are not specified and one having ordinary skill in the art would be unable to discern what units are intended.

Applicants submit that the concept of “equivalent(s)” is a fundamental one in chemical practice and has long been used in acid-base chemistry as a more general expression than “mole(s)” to describe the amount of base required for acid neutralization. Applicant notes that the concept of “equivalent(s)” when applied to bases recognizes that some bases are dibasic or tribasic, etc., meaning that one mole of base can neutralize two or three, etc. moles of H^+ , and therefore one mole of base can correspond to two or three, etc. equivalents, respectively. Thus for bases, the terms “equivalent” and “equivalents” relate to their acid-neutralizing capability. Applying this fundamental concept to the language relating to component (iii) in Claim 1, Applicant notes that the minimum amount of inorganic base recited relates to “50 equivalent % of base”; and Applicant submits that one skilled in the art recognizes that the insertion of “equivalent” into this expression means that the percentage of base is to be calculated based not on the number of moles of base but instead the number of equivalents of base relative to the sulfonamide herbicide free acid. Therefore, for example, a dibasic base may provide twice the equivalent % of base than mole % of base relative to sulfonamide, provided the pK_a associated with each equivalent meets the pK_a limitation recited in the claim.

The only recitation of “units” in Claim 1 is in the expression “2.1 units” relating to numeric difference between the conjugate acid pK_a of the base and the highest pK_a of the

sulfonamide herbicide free acid component. Applicants note that while pK_a values are often described as “ pK_a units”, pK_a units are actually dimensionless (i.e., they are pure numbers). Further, Applicant notes that “equivalent %” like all percentages relates to a ratio and thus does not have physical units either. Accordingly, Applicant submits that units for pK_a s and equivalent percentages would not be expected by one skilled in the art; and the fact that units are not specified for these parameters in no way renders them indefinite.

Applicants further note that the claim language is further explained on page 4, lines 3–11, and amply illustrated with example calculations on page 5, line 3 to page 6, line 2. As indicated in the example where the total number of moles of the indicated sulfonamide herbicides in free acid form was two moles, 50 equivalent % of an inorganic base would require one equivalent of base having the required pK_a value. Analogously, it would be clear to one of ordinary skill that for the same sulfonamide component 75 equivalent % of an inorganic base would require 1.5 equivalents of base having the required pK_a value; and 100 equivalent % of an inorganic base would require 2 equivalents of base having the required pK_a value. As described in the specification, not all base equivalents potentially provided by a dibasic base such as carbonate (CO_3^{2-}) or tribasic base such as phosphate (PO_4^{3-}) may count towards providing the specified “equivalent % of base”, because they may not have strong enough basicity relative to the sulfonamide herbicide free acids (i.e., they may not have the required pK_a value). Applicants submit that these calculations and the concepts upon which the calculations are founded are readily understood by one of ordinary skill, especially in light of the description and examples provided in the present application.

III.

In the Office Action, claims 1-16 were rejected under 35 U.S.C. 103 (a), as unpatentably obvious when U.S. Patent No 5,474,971 to Sandell is considered in view of U.S. Patent No. 5,270,288 to Riebel et al. and U.S. Patent 6,258,749 to Nonomura. The Office Action maintained that Sandell teaches a process for preparing a rapidly disintegrating water-dispersible granular composition, comprising extruding a premix through a die or screen at elevated temperature without using any water (column 1, lines 37-38 and 56-59 were cited); that Sandell teaches a process comprising extruding a dry premix comprising by weight 0.01-90% of one or more active ingredients, 1-60% one or more diluents, 0-30% binders and two or more additives ranging from 0-80% through a die to form granules (column 4, lines 25-45 were cited); that the active ingredients disclosed in Sandell include sulfonamides such as sulfometron-methyl (column 10, Table 1, Compound No. 63 was cited); that Sandell also teaches sodium and potassium carbonates as optional additives/gas generating agents (column 14, lines 39-40 were cited); and that Sandell further teaches conventional methods for preparing water-dispersible granule compositions which include extrusion of a water-wet

paste (column 3, lines 59-62). The Office Action further maintained that Nonomura teaches methods and formulations for treating plants and enhancing growth (the abstract was cited); that the use of any polyacylpolysaccharide or polyalkylpolysaccharide and herbicides is disclosed in Nonomura as well (column 8, line 47 and column 15, lines 30-33 were cited); and that Reibel et al. teaches the combination of arylsulfonylureas with the sulfonamides thifensulfuron-methyl and tribenuron-methyl in formulated pastes (column 1, lines 6-16; column 4, line 32; and column 5, lines 57-58 were cited).

The Office Action (noting that water is omitted from the process disclosed by Sandell, which discloses a method which does not require the addition of water to form the water-dispersible granule) maintained that water is a commonly used diluent in processes that require a wetter texture. The Office Action (noting that Sandell does not specifically teach the use of the base sodium phosphate) maintained that bases are broadly taught as being additives within the disclosed process. The Office Action (noting that the addition of a saccharide is not disclosed by Sandell) maintained that Sandell broadly discloses the addition of binders with additives within the process. The Office Action (noting that Nonomura does not teach a process of making a paste-extruded sulfonamide herbicide) maintained that saccharides are disclosed as being additives to formulations used to improve plant growth. The Office Action (also noting that the specific sulfonamides thifensulfuron-methyl and tribenuron-methyl are not specifically taught in Sandell) maintained that various other sulfonamides such as bensulfuron methyl, chlorimuron ethyl and chlorsulfuron are taught in Sandell (Table 1, compounds 4, 9 and 11 were cited); that Sandell discloses that one or more active ingredients including herbicides may be used; and that Reibel et al. teaches that thifensulfuron-methyl and tribenuron-methyl may be used in combination with other herbicidally-active ingredients. The Office Action (noting that a step of sifting the dried extrudate is not disclosed) maintained that sifting as a step commonly used in process in order to remove excess dusts and products that are too small in size for retail purposes.

The Office Action also concluded that it would have been obvious to one of ordinary skill in the art at the time of the invention:

A. to combine the teachings of Sandell to further include water in a process for preparing the paste-extruded sulfonamide (the Office Action suggested that one would have been motivated to include water because adding water would help form a paste and if the composition extruded was too powdery, adding water would improve the texture).

B. to combine the teachings of Sandell to further include potassium phosphate and sodium phosphate(dodecahydrate) in a process for preparing the paste-extruded sulfonamide (the Office Action suggested that one would have been motivated to include potassium

phosphate and sodium phosphate(dodecahydrate) because they are common bases used in chemical synthesis and preparation).

C. to combine the teachings of Sandell with Nonomura to further include a saccharide (the Office Action suggested that one would have been motivated to include a saccharide because saccharides are commonly used binders and dispersants and therefore constitute additives well known to one having ordinary skill in the art).

D. to combine the teachings of Sandell with Reibel et al. to further include mixtures including the sulfonamides thifensulfuron-methyl and tribenuron-methyl (the Office Action suggested that one would have been motivated to include thifensulfuron-methyl and tribenuron-methyl because they are sulfonamides and have a similar core structure and similar function to sulfometuron-methyl).

E. to combine the teachings of Sandell to further include the step of sifting the dried extrudate (the Office Action suggested that one would have been motivated to include the step of sifting because it would remove excess powder to ensure the end product was properly formed and enable consistent weight of the final product before packaging).

The Office Action suggested that claims 1-16 were rejected based on these conclusions.

As indicated in its title, Sandell relates to water-dispersible granular agricultural compositions made by heat extrusion (emphasis added). Applicants submit that while Sandell mentions extrusion of a water-wet paste at column 3, line 62, this mention is by way of contrast (see also column 1, lines 23-27); and that the Sandell teachings with regard to compositions made by extruding a dry premix using a heat extrusion technique are clearly not meant to apply to extrusion of a water-wet paste. Applicants note that Sandell describes at column 13, lines 13-17 a water-soluble diluent component which melts or softens at elevated temperatures and acts as the primary extrusion aid; and that Sandell further describes at column 13, lines 36-48 the use of heat-activated binders capable of acting as a binder and extrusion aid when heat is applied. Applicants submit that one of ordinary skill in the art would understand from Sandell that components such as these would aid in developing the texture suitable for the heat extrusion. Accordingly, Applicants submit that rather than concluding that water should be added to the dry premix used in the Sandell process to improve texture as suggested in the Office Action, one of ordinary skill in the art would instead conclude that the addition of water to provide a water-wet paste suitable for use in paste extrusion would be detrimental to the preparation of the premixes to be used in the heat extrusion process taught in Sandell. Indeed, Applicants note that the Abstract of Sandell states "No water is added in the process thereby eliminating the need for drying".

Applicants further submit that neither Nonomura nor Reibel et al. fairly suggest that the Sandell teachings with regard to compositions made by extruding a dry premix using a heat extrusion technique should somehow apply as well to extrusion of a water-wet paste.

Moreover, as discussed above, Applicants have disclosed an claimed a process which involves, in part, preparing a mixture which comprises amongst its claimed components a sulfonamide herbicide free acid component and an advantageous amount (at least about 50 equivalent % in Claim 1) of base selected from inorganic base equivalents having conjugate acid pK_a s at least 2.1 units greater than the highest pK_a of the sulfonamide herbicide free acid component. Applicants submit that Sandell does not disclose or suggest this advantageous combination. Although there are sulfonylurea herbicides listed among the active ingredients in Table 1 of Sandell, Applicant submits that Sandell does not fairly suggest adding an advantageous amount of base selected from inorganic base equivalents having conjugate acid pK_a s at least 2.1 units greater than the highest pK_a of any sulfonamide herbicide free acid component which might be used in the Sandell invention. Indeed, Applicants note a complete reading of the entire paragraph of column 14, lines 37–41 teaches the optional use of gas producing disintegrants for faster breakup of the granule in water, and combinations of sodium and potassium bicarbonates and carbonates with acids such as citric and fumaric acid as examples of suitable gas generating additives. Applicants submit that there is no suggestion of adding a suitable base in an advantageous amount relative to a sulfonamide herbicide free acid component. In addition, Applicants submit that one of ordinary skill would clearly not conclude from Sandell that these gas generating additives should be used in a water-wet paste prior to extrusion.

Applicants further submit that neither Nonomura nor Reibel et al. fairly suggest that the preparation of a Sandell premix should include adding an advantageous amount of base selected from inorganic base equivalents having conjugate acid pK_a s at least 2.1 units greater than the highest pK_a of any sulfonamide herbicide free acid component which might be used in the Sandell invention.

In sum, Applicants submit that Claims 1-16 is patentable over Sandell, even in light of the teachings of Reibel et al. and/or Nonomura.

IV.

In the Office Action, Claims 17 was rejected under 35 U.S.C. 103 (a), as unpatentably obvious in light of Sandell. The Office Action maintained that Sandell teaches a rapidly disintegrating water-dispersible granular composition (column 1, lines 37-38 and 56-59 were cited); that Sandell teaches a process comprising by weight 0.01-90% of one or more

active ingredients, including sulfonamides such as sulfometron-methyl (Table 1, Compound No. 63 was noted), 1-60% one or more diluents, 0-30% heat activated binders and two or more additives (0-80% through a die to for granules (column 4, lines 25-45 were noted; that Sandell teaches the bases sodium and potassium carbonates (column 14, lines 39-40 were noted); and (noting that Sandell does not teach the addition of water) that it would have been obvious to one of ordinary skill in the art at the time of the invention to combine the teachings of Sandell to further include water (the Office Action suggested that one would have been motivated to include water because adding water would help the composition to be extruded and formed by improving its texture).

Claim 17 relates to a paste-extruded sulfonamide herbicide composition prepared by the process of Claim 1; and Claim 1 clearly relates to a process which involves, in part, preparing a mixture which comprises amongst its claimed components sufficient water to make the mixture an extrudable paste. Applicants submit that the extrusion of a dry premix as taught in of Sandell does not result in a paste-extruded composition of the type claimed in Claim 17. Moreover, although there are sulfonylurea herbicides listed among the active ingredients in Table 1 of Sandell, Applicants submit that Sandell does not fairly suggest using suitable bases in advantageous amounts relative to a sulfonamide herbicide free acid component. Accordingly, Applicants submit that of Sandell does not disclose or fairly suggest paste-extruded sulfonamide herbicide compositions of the type claimed in Claim 17.

In view of the foregoing, allowance of the above-referenced application is respectfully requested.

Respectfully submitted,



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THE CHEMIST'S COMPANION

A Handbook of Practical
Data, Techniques, and References

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4. Other Heterocycles

Five-ring compounds with ≥ 1 heteroatom are covered in references 6c and 6d. General data and references on tautomerism of nucleic acid bases are found in reference 23.

F. References

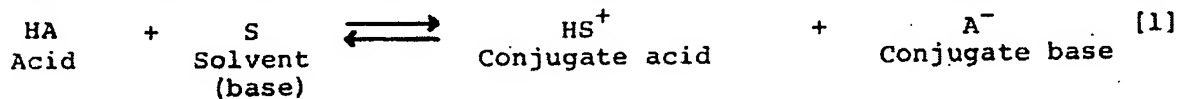
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IX. ACIDS AND BASES

A. Introduction

1. Bronsted Acid-Base Concept (1,2)

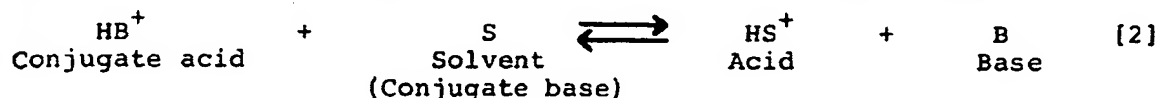
The Bronsted acid-base concept is defined in terms of proton transfer equilibria. Hence an acid in the Bronsted sense must possess at least one



acidic hydrogen atom; a base is simply a proton acceptor. The strength of an acid is measured in terms of the equilibrium constant (K) for the proton

Refs. p. 79.

transfer reaction; the stronger the acid, the greater the value of K (see below). In discussing base strength, it is conventional to refer to the strength of the conjugate acid, that is the protonated base:



In each case, distinction must be made between the thermodynamic equilibrium acidity constant, K_a , and the concentration equilibrium acidity constant, K_c . The former is the true measure of equilibrium, while the latter is the value usually measured experimentally, especially in solutions that are not very dilute. For the example in equation [1], under the usual conditions of small concentrations of acid (thus concentration or activity of solvent is virtually constant):

$$K_a = K'_a(a_S) = \frac{(a_{A^-})(a_{\text{HS}^+})}{(a_{\text{HA}})} = \frac{(c_{A^-})(c_{\text{HS}^+})}{(c_{\text{HA}})} \cdot \frac{\gamma_{\pm}^2}{\gamma_{\text{HA}}}$$

$$K_c = K'_c(c_S) = \frac{(c_{A^-})(c_{\text{HS}^+})}{(c_{\text{HA}})}$$

where a = activity, c = molar concentration, and γ = activity coefficient. Activity, a , may be considered an "effective" concentration, one that correctly represents the actual behavior of real species under the usual nonideal conditions, as contrasted to the measured concentration, c . By definition, γ = unity in the standard state, which is a solution of unit concentration with the same properties as a solution of infinite dilution (Debye-Hückel conditions). Thus it is possible to determine the classical constant, K_c at a series of concentrations as a function of ionic strength, μ , and extrapolate to $\mu = 0$ to obtain K_a ($\mu = 1/2 (\sum c_i Z_i^2)$, c_i = molar concentration of an ion of charge Z_i , summation for all ions present).

Since K_a values vary over many orders of magnitude, it is more convenient to use $\text{p}K_a$ values:

$$\text{p}K_a = -\log_{10} K_a$$

Clearly, the stronger the acid, the smaller the value of $\text{p}K_a$; conversely, for bases, the smaller the $\text{p}K_a$ of the conjugate acid (BH^+), the weaker is the base (B). One can also discuss base strength directly, as in the following equation, using water as solvent-acid:



$$K_b = \frac{(a_{\text{HB}^+})(a_{\text{HO}^-})}{(a_{\text{B}})}$$

K_b values are less common than the K_a values of the conjugate acid; to convert pK_a to pK_b , it is necessary to know the autoionization constant for the solvent, K_w in this case:

$$pK_a + pK_b = pK_w$$

Values of pK_w are 14.944 (0°), 14.167 (20°), 13.997 (25°), 13.680 (35°), and 13.017 (60°).

Another measure of the Bronsted "acidity" of a dilute aqueous solution is the activity of hydrogen ions, commonly denoted as the pH ($= -\log_{10} a_{H_3O^+}$). In practice, it is impossible to determine independently the activity of hydronium ion in a given solution, and accurate values must be measured relative to a standard. The United States pH scale is based on the pH values of a series of standard solutions, measured with a Pt, $H_2(g)|$ buffer, $Cl^-|AgCl, Ag$ cell (3a). The British scale is based on potassium hydrogen phthalate solutions as the primary standard (4).

In the special case of acid catalyzed ionization of alcohols to carbonium ions, $H_3O^+ + ROH \rightleftharpoons R^+ + 2H_2O$, the strength of the alcohol as a base is denoted by pK_{R^+} , defined as the pH of the solution when the alcohol is half-ionized: $pK_{R^+} = pH$ when $(c_{R^+})/(c_{ROH}) = 1$. (5)

2. Lewis Acid-Base Concept (1,6,7)

A Lewis acid is any substance that will accept an electron pair from an electron pair donor (Lewis base); a Lewis acid must necessarily possess an unfilled orbital. The types of Lewis acids (bases) are classified as follows:

(a) Protons and metal cations. As the charge and electronegativity of the metal increases, the acid strength increases; if a metal has more than one oxidation state, the highest is the most active (Sb^{+5} , Sn^{+4} , Fe^{+3} , etc.).

(b) Molecules with ≥ 1 vacant orbital on a central atom, such as compounds of Group II and III elements (BX_3 , AlX_3 , BeX_2 , ZnX_2 , etc.) are the most common Lewis acids. It is noteworthy that vigorously anhydrous $AlCl_3$ and other Lewis acids are relatively inactive as catalysts unless a "co-catalyst," such as small amounts of HX or H_2O , is present.

(c) Molecules with unsaturation. Double and triple bonds react as Lewis bases toward electrophilic (Lewis acid) species, as in Friedel-Crafts reactions.

Unlike the pK and pH scales for Bronsted acids, no satisfactory general quantitative scale of Lewis acid strength has been developed, especially since the relative order of strengths is highly dependent on the reference base (6,7). SbF_5 is generally considered to be the strongest Lewis acid. Recently an "optical scale" for Lewis basicity has been developed for oxide systems (J. A. Duffy and M. D. Ingram, J. Amer. Chem. Soc., 93, 6448 (1971)).

B. Solvent Effects (8,9)

One of the most important factors determining acid (base) strength is the solvent used, especially when the solvent is a participant in the equilibrium as is generally the case. Changing solvents results in changes not only in acidity constants, but often also in the order of relative acidities of a series of compounds. A dramatic example is provided by the recent data obtained on gas phase acidities (10), which showed for aliphatic alcohols an acid strength order of primary < secondary < tertiary, the reverse of typical solution measurements. In addition, toluene was found to have an acid

strength between that of methanol and ethanol. Similar findings have been reported for gas phase amine acidity and basicity (10).

There are many reasons why solvents other than water are used in acid-base determinations: (1) solubility problems; (2) leveling effect (all acids measured appear to have the same strength; this effect is more serious for more basic (acidic) solvents); (3) acid or base strength of substance is beyond the range measurable in water (the strongest base capable of existence in significant concentration in water is hydroxide ion; the conjugate base of any solvent is the strongest base existing in that solvent). Ideally, solvents for acid-base determinations should (a) be both weakly acidic and weakly basic, (b) have a high dielectric constant to promote ionization, (c) be unreactive with the substances involved, including indicators, and (d) be easily obtainable in pure form. The following lists of recommended solvents are taken from (9).

Determination of Acids

Inert solvents (in order of decreasing dielectric constant): acetonitrile, acetone, ethyl methyl ketone, i-butyl methyl ketone, chlorobenzene, toluene, benzene.

Basic or amphoteric solvents (in order of increasing basicity): propylene glycol, methyl cellosolve, methanol, ethanol, 1-butanol, 1-propanol, 2-propanol, t-butyl alcohol, diethyl ether, p-dioxan, DMF, pyridine, 1-butyamine, ethylenediamine.

Determination of Bases

Inert solvents (in order of decreasing dielectric constant): acetonitrile, acetone, ethyl methyl ketone, i-butyl methyl ketone, chlorobenzene, chloroform, benzene, carbon tetrachloride, p-dioxan, cyclohexane, hexane.

Acid or amphoteric solvents (in order of increasing acidity): 2-propanol, cellosolve, propylene glycol, ethylene glycol, nitrobenzene, nitromethane, acetic anhydride, propionic acid, acetic acid, formic acid.

Some specific examples of the ranges available for measurable pK_a values are as follows (referred to water): ammonia (2 to 22), water (0 to 14), ethanol (-4 to 18), diethyl ether (-7 to 40), acetic acid (-8 to 11), formic acid (-9 to 7), sulfuric acid (-16 to -10), heptane (-20 to 40).

The meaning of pH changes considerably in nonaqueous media, and even in aqueous media at high concentrations of electrolytes. For solutions whose ionic strength is $>0.1M$, pH as a measure of acidity breaks down. Other scales have been developed, such as the Hammet acidity function; these are described in a separate section below. Recently, Bates has discussed approaches to measurement of pH for mixed aqueous solvents (3b).

C. Acidity Constants

1. General Guide To The Literature

It is impractical to include an exhaustive collection of acidity data in this book. In addition to the key references given within the tables below, the following bibliography to specific compound types is offered.

Compound Type or Study	Ref.
Prediction of acid and base strengths of organic compounds using Hammett σ, ρ relationships	11
Basicity of carbonyl compounds	12
Weak organic bases, (alkenes; alkynes; aromatics; halogen compounds; compounds of N, O, S, P, and other elements)	13
Acidity of phenols	14
Basicity of aromatics	15
Heterocyclic compounds	16
Hydrocarbon acidity	17, 18
Acidity of benzenesulfonamides	19
Equilibrium acidities in dimethyl sulfoxide	20
General collections of large amounts of acid-base data	2, 21

2. Dissociation Constants of Common Acids in Water

These data were taken primarily from references 2, 22, and 23. The first ionization of sulfuric acid is too high to measure accurately, as are those for HCl, HI, HClO₃, and so on. For information on extremely strong ("super") acids, see page 21.

Acid	T(°C)	K _a	pK _a
Acetic (CH ₃ CO ₂ H)	25	1.754 × 10 ⁻⁵	4.75
Arsenic (H ₃ AsO ₄) (1)	18	5.62 × 10 ⁻³	2.25
(2)	18	1.70 × 10 ⁻⁷	6.77
(3)	18	3.95 × 10 ⁻¹²	11.60
Arsenious (HAsO ₃)	25	6 × 10 ⁻¹⁰	9.23
Benzoic (C ₆ H ₅ CO ₂ H)	25	6.312 × 10 ⁻⁵	4.20
o-Boric (H ₃ BO ₃) (1)	20	7.3 × 10 ⁻¹⁰	9.14
(2)	20	1.8 × 10 ⁻¹³	12.74
(3)	20	1.6 × 10 ⁻¹⁴	13.80
n-Butyric (C ₃ H ₇ CO ₂ H)	25	1.515 × 10 ⁻⁵	4.82
Carbonic (H ₂ CO ₃) (1)	25	4.30 × 10 ⁻⁷	6.37
(2)	25	5.61 × 10 ⁻¹¹	10.25
Chloroacetic (ClCH ₂ CO ₂ H)	25	1.359 × 10 ⁻³	2.87
Chromic (H ₂ CrO ₄) (1)	25	1.8 × 10 ⁻¹	0.74
(2)	25	3.20 × 10 ⁻⁷	6.49
p-Cresol (CH ₃ C ₆ H ₄ OH)	25	5.5 × 10 ⁻¹¹	10.26
Formic (HCO ₂ H)	20	1.77 × 10 ⁻⁴	3.75
Hydriodic (HI)	25	~1.0 × 10 ⁺¹¹	~ -11
Hydrobromic (HBr)	25	~1.0 × 10 ⁺⁹	~ -9
Hydrocyanic (HCN)	25	4.93 × 10 ⁻¹⁰	9.31
Hydrofluoric (HF)	25	3.53 × 10 ⁻⁴	3.45
Hydrogen selenide (H ₂ Se)	25	1.0 × 10 ⁻⁴	4.0
Hydrogen telluride (H ₂ Te)	25	1.0 × 10 ⁻³	3.0

Refs. p. 79.

(Continued)

Acid	T(°C)	K _a	pK _a
Hydrogen sulfide (H ₂ S) (1)	18	9.1 × 10 ⁻⁸	7.04
(2)	18	1.1 × 10 ⁻¹²	11.96
Hypobromous (HOBr)	25	2.06 × 10 ⁻⁹	8.69
Hypochlorous (HOCl)	18	2.95 × 10 ⁻⁸	7.53
Hypoiodous (HOI)	25	1.0 × 10 ⁻¹⁰	10
Iodic (HIO ₃)	25	1.69 × 10 ⁻¹	0.77
Nitric (HNO ₃)	25	4.36 × 10 ⁺¹	-1.64
Nitrous (HNO ₂)	12.5	4.6 × 10 ⁻⁴	3.37
Octanoic (C ₇ H ₁₅ CO ₂ H)	25	1.28 × 10 ⁻⁵	4.89
Perchloric (HClO ₄)	25	~1.0 × 10 ⁺⁸	~-8
Periodic (HIO ₄)	25	2.3 × 10 ⁻²	1.64
Phenol (C ₆ H ₅ OH)	20	1.28 × 10 ⁻¹⁰	9.99
Picric (2,4,6-(NO ₂) ₃ C ₆ H ₂ OH)	25	4.2 × 10 ⁻¹	0.38
o-Phosphoric (H ₃ PO ₄) (1)	25	7.52 × 10 ⁻³	2.12
(2)	25	6.23 × 10 ⁻⁸	7.21
(3)	18	2.2 × 10 ⁻¹³	12.67
o-Phosphorous (H ₃ PO ₃) (1)	25	1.58 × 10 ⁻²	1.8
(2)	25	6.3 × 10 ⁻⁷	6.2
Pyrophosphoric (H ₄ P ₂ O ₇) (1)	25	1.0 × 10 ⁻¹	1.0
(2)	25	1.0 × 10 ⁻²	2.0
(3)	25	1.0 × 10 ⁻⁷	7.0
(4)	25	1.0 × 10 ⁻⁹	9.0
Sulfanilic (H ₂ NC ₆ H ₄ SO ₃ H)	25	5.9 × 10 ⁻⁴	3.23
Sulfuric (H ₂ SO ₄) (1)	25	~1.0 × 10 ⁺³	~-3
(2)	25	1.20 × 10 ⁻²	1.92
Sulfurous (H ₂ SO ₃) (1)	18	1.54 × 10 ⁻²	1.82
(2)	18	1.02 × 10 ⁻⁷	6.91
Trifluoroacetic (CF ₃ CO ₂ H)	25	5.9 × 10 ⁻¹	0.23

3. Dissociation Constants of Common Nitrogen Bases in Water

These data were taken from references 16 and 24. K_a and pK_a refer to the conjugate acid; a large value of pK_a means a strong base.

Base	T(°C)	K _a	pK _a
Ammonia	25	5.66 × 10 ⁻¹⁰	9.247
Aniline	25	2.34 × 10 ⁻⁵	4.630
1,8-Bis(dimethylamino) naphthalene ^a	25	4.27 × 10 ⁻¹³	12.37
Benzylamine	25	4.67 × 10 ⁻¹⁰	9.33
n-Butylamine	20	1.67 × 10 ⁻¹¹	10.777
Cyclohexylamine	24	2.19 × 10 ⁻¹¹	10.66
Diethylamine	20	8.13 × 10 ⁻¹²	11.090
Diisopropylamine	21	7.41 × 10 ⁻¹²	11.13
Dimethylamine	25	1.85 × 10 ⁻¹¹	10.732
Diphenylamine	25	1.62 × 10 ⁻¹	0.79
Ethylamine	20	1.56 × 10 ⁻¹¹	10.807

Refs. p. 79.





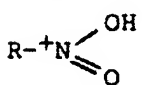
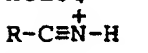
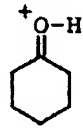
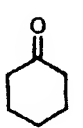
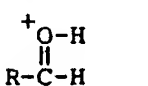
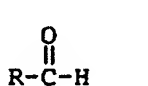
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Base	T(°C)	K _a	pK _a
Ethylenediamine (1)	20	8.41 x 10 ⁻¹¹	10.075
(2)	20	1.04 x 10 ⁻⁷	6.985
Hexamethylenediamine (1)	20	7.85 x 10 ⁻¹²	11.105
(2)	20	9.68 x 10 ⁻¹¹	10.014
Isoquinoline	20	4.17 x 10 ⁻⁶	5.38
Methylamine	25	2.70 x 10 ⁻¹¹	10.657
N-methylaniline	25	1.41 x 10 ⁻⁵	4.848
Morpholine	25	4.67 x 10 ⁻⁹	8.33
Piperazine (1)	23.5	1.48 x 10 ⁻¹⁰	9.83
(2)	23.5	2.76 x 10 ⁻⁶	5.56
Piperidine	25	7.53 x 10 ⁻¹²	11.123
Purine	20	4.07 x 10 ⁻³	2.39
Pyrazine (1)	27±2	2.24 x 10 ⁻¹	0.65
Pyridine	25	6.17 x 10 ⁻⁶	5.21
Pyrimidine	20	2.24 x 10 ⁻¹	0.65
Pyrrolidine	25	5.37 x 10 ⁻¹²	11.27
Quinoline	25	1.35 x 10 ⁻⁵	4.87
o-Toluidine	25	3.55 x 10 ⁻⁵	4.45
m-Toluidine	25	1.86 x 10 ⁻⁵	4.73
p-Toluidine	25	8.32 x 10 ⁻⁶	5.08
Triethylamine	18	9.77 x 10 ⁻¹²	11.01
Trimethylamine	25	1.55 x 10 ⁻¹⁰	9.81
Urea	21	7.94 x 10 ⁻¹	0.10

^aSold under the trade name "Proton Sponge." It has unusual properties for use in organic chemical reactions (Aldrich Chemical Company).


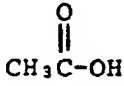
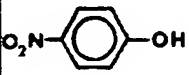
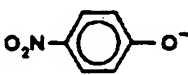
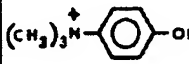
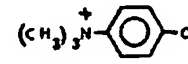
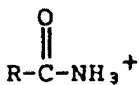
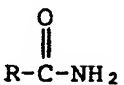
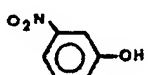
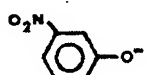
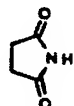
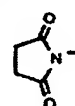
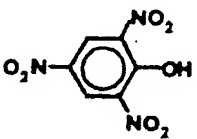
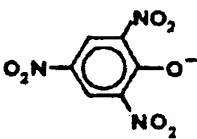
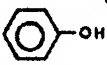
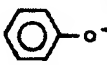
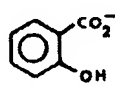
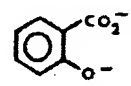
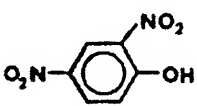
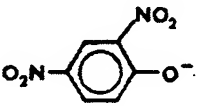


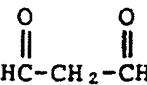
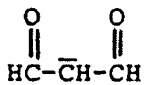


4. Approximate pK_a Values for Common Reagents

The values in this table are meant only to be representative and to give some information on the effect of structure on acidity. The values above pK_a = 15 and below -2 are quite approximate, as indicated by the significant figures shown. These values of course are dependent on solvent, and in some cases the order of relative acidities may even change. These data were taken primarily from references 22 and 23.








Conjugate Acid	Conjugate Base	pK _a	Conjugate Acid	Conjugate Base	pK _a
SbF ₅ ·FSO ₃ H	SbF ₅ ·FSO ₃ ⁻	<-20			-7.4
HPF ₆	PF ₆ ⁻	-20			-7
	RNO ₂	-12	ArSO ₃ H	ArSO ₃ ⁻	-7
HClO ₄	ClO ₄ ⁻	-10	HCl	Cl ⁻	-7
	RCN	-10			-7
HI	I ⁻	-10			
		-8			

Refs. p. 79.

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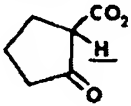
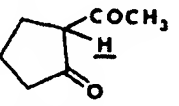
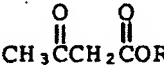
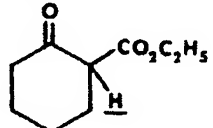

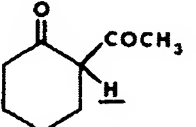
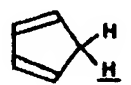
Conjugate Acid	Conjugate Base	pK _a	Conjugate Acid	Conjugate Base	pK _a
ArS ⁺ H ₂	ArSH	-7	H ₂ CO ₃	HCO ₃ ⁻	6.35
ArO ⁺ H ₂	ArOH	-7	H ₂ S	HS ⁻	7.00
		-6.5			7.2
(CH ₃) ₂ SH ⁺	(CH ₃) ₂ S	-5.2	ArSH	ArS ⁻	8
(CH ₃) ₂ OH ⁺	(CH ₃) ₂ O	-3.5			8
CH ₃ OH ₂ ⁺	CH ₃ OH	-2	CH ₃ CH ₂ NO ₂	CH ₃ CH ₂ NO ₂ ⁻	8.5
t-BuOH ₂ ⁺	t-BuOH	-2	HCN	CN ⁻	9.1
HNO ₃	NO ₃ ⁻	-1.4	NH ₄ ⁺	NH ₃	9.24
		-1			9.3
CF ₃ CO ₂ H	CF ₃ CO ₂ ⁻	0			9.6
		0.4			9.98
CCl ₃ CO ₂ H	CCl ₃ CO ₂ ⁻	0.9	RNH ₃ ⁺	RNH ₂	~10
CHCl ₂ CO ₂ H	CHCl ₂ CO ₂ ⁻	1.3	R ₂ NH ₂ ⁺	R ₂ NH	
(C ₆ H ₅ SO ₂) ₂ NH	(C ₆ H ₅ SO ₂) ₂ N ⁻	1.45	R ₃ NH ⁺	R ₃ N	
CH ₂ ClCO ₂ H	CH ₂ ClCO ₂ ⁻	2.8	C ₆ H ₅ SO ₂ NH ₂	C ₆ H ₅ SO ₂ NH ⁻	10.1
HF	F ⁻	3.17	CH ₃ NO ₂	CH ₂ NO ₂ ⁻	10.2
HNO ₂	NO ₂ ⁻	3.29	HCO ₃ ⁻	CO ₃ ²⁻	10.33
CH ₂ (NO ₂) ₂	CH(NO ₂) ₂ ⁻	3.6			13.4
HCO ₂ H	HCO ₂ ⁻	3.7	(RO ₂ C) ₂ CH ₂	(RO ₂ C) ₂ CH ⁻	13
		4			15
ArNH ₃ ⁺	ArNH ₂	4	H ₂ O	OH ⁻	15.7
		5	CH ₃ OH	CH ₃ O ⁻	16
CH ₃ CO ₂ H	CH ₃ CO ₂ ⁻	5			
		5.2			

(Continued)

Conjugate Acid	Conjugate Base	pK _a	Conjugate Acid	Conjugate Base	pK _a
CH ₃ CH ₂ OH	CH ₃ CH ₂ O ⁻	18			25
PhC≡C-H	PhC≡C ⁻	18.5	Ph ₃ CH	Ph ₃ C ⁻	31.5
t-BuOH	t-BuO ⁻	19	PhCH ₃	PhCH ₂ ⁻	35
		20	NH ₃	NH ₂ ⁻	36
CH ₃ SO ₂ CH ₃	CH ₃ SO ₂ CH ₂ ⁻	23	CH ₂ =CH ₂	CH ₂ =CH ⁻	36.5
HC≡CH	HC≡C ⁻	25		C ₆ H ₅ ⁻	37
		25	CH ₄	CH ₃ ⁻	40


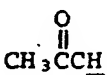
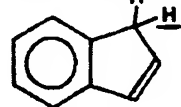

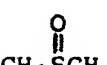
5. Approximate Acidities of Carbon Acids

A carbon acid has been defined as "an organic substance that, when tested with a suitable base, donates a proton to that base by fission of a carbon-hydrogen bond" (18). Because of the very weak nature of these acids (pK > 15) direct measurement of equilibrium (thermodynamic) acidities is subject to large error. Several methods have been used to make such measurements; for specific details consult the references shown. The values reported here are meant only to be guides to the relative acidities of the different compounds and might change considerably with solvent. Reference 17 is a general review of the field.

Compound	pK _a	Ref.	Compound	pK _a	Ref.
O ₂ NCH ₂ NO ₂	3.6	25	CH ₃ NO ₂	10.6	25
O ₂ NCH ₂ CO ₂ CH ₃	5.8	25		10.5	25
	8	25		11	25
CH ₃ CH ₂ NO ₂	8.6	25		11.5	25
NCCH ₂ CO ₂ C ₂ H ₅	9	25	NCCH ₂ CN	11-12	25
	9	25	RO ₂ CCH ₂ CO ₂ R		25
	10	25		14-15	26

Refs. p. 79

(Continued)

Compound	pK _a	Ref.	Compound	pK _a	Ref.
PhC≡C-H	18.5	27	Ph ₂ CH ₂	33	28
	19	27	PhCH ₃	35	18
	20	25	CH ₂ =CH-CH ₃	35.5	18
	21	27	H ₂ C=CH ₂	36.5	18
CH ₃ CO ₂ ⁻	24	25	Benzene	37	18
RO ₂ CCH ₂ R	24.5	25	Cyclopropane	39	18
CH ₃ CN	25	25	CH ₄	40	18
	25	25	CH ₃ CH ₃	42	18
	31.3	18	Cyclobutane	43	18
Ph ₃ CH	31.5	28	CH ₃ CH ₂ CH ₃	44	18
			Cyclopentane	44	18
			Cyclohexane	45	18

6. Hammett and Other Acidity Functions (31,32,33)

a. Theory: The activity and concentration of hydrogen ion are routinely determined via pH measurements, but such measurements only have accurate meaning in very dilute solutions, in a single solvent, usually water. In concentrated solutions or in nonaqueous or mixed solvent systems some other parameter is necessary to measure the acidity of a solution. An acidity function is thus a measure of the proton donating ability of a medium, and is important in kinetic investigations of acid (or base) catalyzed reactions.

The best known and most widely used such function is the Hammett acidity function, H_0 , which is the best function for comparing acidities of different media and is far superior to simple stoichiometric acid concentration:

$$H_0 = pK_{HB} + \log \frac{C_{HB^+}}{C_B} = -\log \frac{a_{H^+} \gamma_B}{\gamma_{HB^+}} = -\log h_0$$

Ideally, H_0 represents a unique value for a particular acid solution, say 85% H₂SO₄ (a comparable D_0 is also possible for D₂SO₄/D₂O); further, an H_0 scale should exist that would be a function of H₂SO₄ concentration. Note that $H_0 \rightarrow pH$ for dilute, aqueous solutions. Such a scale was developed by using a series of so-called indicator bases, B, weak bases for which the extent of protonation (or deprotonation) in strong acids could be measured easily (e.g., spectrophotometrically). Then -- again ideally -- having measured H_0 with a series of weak bases of different strengths, the extent of

ionization for any other weak base should correspond to the equation above; thus a plot of $\log(c_{HB^+}/c_B)$ against H_0 should be linear with slope of -1.00 for all neutral bases (proton acceptors). If this were true, an H_0 scale would depend only on the specific acid solution, and would be independent of the indicators (bases) used to measure it; for this to be true, the ratio (γ_B/γ_{HB^+}) and its dependence on acid concentration must be the same for all neutral bases in a given acid solution. In practice these assumptions are not met with all bases, and the "Hammett acidity function" applies only to any H_0 scale derived originally from measurements of ionization of certain primary amine indicators (mainly substituted anilines). By definition, a Hammett base is one whose values of $\log c_{HB^+}/c_B$ plotted against H_0 do give a straight line with a slope of unity; they need not be amines and can have any structure. Acidity functions defined by non-Hammett bases have also been derived and have other symbols, as shown by the following examples.

Function	System
$H_- = -\log \frac{(a_{H^+})(\gamma_{B^-})}{\gamma_{HB}}$	When base is negatively charged (not neutral), as for $BH^+ B^- + H^+$, where BH is a neutral, acid indicator
$J_O = -\log \frac{(a_{H^+})(\gamma_{ROH})}{(a_{H_2O})(\gamma_{R^+})} = H_0 + \log a_w$	This Gold and Hawes function (also referred to as C_O and H_R) applies to equilibria between alcohols and carbonium ions
$H_+ = -\log \frac{(a_{H^+})(\gamma_{HR^+})}{\gamma_{H_2 R^{+2}}}$	A measure of ability of medium to transfer a proton to a cationic base, HR^+ to form the conjugate acid, H_2R^{+2}

There are many others (H_0 , H_A , H_I , etc.) introduced for specific reaction systems; for details and data consult references 31 to 33.

b. Some H_0 Data for Aqueous Acids at 25°: The following tables were taken mainly from references 31 and 32, where considerably more data are available. Temperature dependence data of H_0 for aq H_2SO_4 may be found in reference 34. The table headings have the following meaning: % = weight percent acid (g/100 g solution), M = acid molarity (moles/l), m = acid molality (moles/1000 g solvent), a_w = activity of water. Some recent determinations have been made of H_0 values for "super-acid" systems (acidity greater than 100% H_2SO_4); see reference 37.

ϕ	$-H_o$	M	m	a_w
<u>Hydrochloric Acid</u>				
3	0.13	0.83	0.85	0.961
6	0.58	1.69	1.71	0.919
9	0.90	2.57	2.71	0.865
12	1.21	3.48	3.74	0.801
15	1.54	4.41	4.83	0.730
18	1.87	5.37	6.04	0.649
22	2.35	6.69	7.75	0.531
26	2.87	8.05	9.65	0.419
30	3.39	9.45	11.76	0.317
34	3.95	10.90	14.14	0.225
36		11.64	15.40	0.186
40		13.15	18.32	0.121

<u>Sulfuric Acid</u>				
5	0.02	0.520	0.540	
10	0.31	1.085	1.13	0.956
15	0.66	1.685	1.79	0.923
20	1.01	2.32	2.55	0.879
25	1.37	3.00	3.39	0.824
30	1.72	3.73	4.37	0.752
35	2.06	4.49	5.48	0.666
40	2.41	5.31	6.80	0.564
45	2.85	6.18	8.34	0.459
50	3.38	7.11	10.19	0.352
55	3.91	8.095	12.45	0.251
60	4.46	9.16	15.30	0.160
65	5.10	10.28	19.12	0.091
70	5.80	11.48	23.5	0.050
75	6.56	12.75	30.6	0.018
80	7.34	14.07	40.8	0.005
85	8.14	15.40	57.7	0.002
90	8.92	16.65	91.6	0.0003
95	9.85	17.76	193.5	
98	10.27			
99	10.57			
99.5	10.83			
99.9	11.42			
100.0	11.94			

Perchloric Acid

5	-0.02	0.51	0.523	0.980
10	0.35	1.05	1.100	0.956
15	0.63	1.62	1.765	0.925
20	0.95	2.23	2.49	0.890
25	1.25	2.88	3.32	0.840
30	1.60	3.58	4.26	0.770
35	1.97	4.34	5.36	0.685

$\%$	$-H_2O$	M	m	a_w
<u>Perchloric Acid</u>				
40	2.40	5.15	6.63	0.580
45	2.92	6.02	8.15	0.460
50	3.52	6.98	9.95	0.330
55	4.22	8.01	12.10	0.200
60	5.25	9.13	14.92	0.110
65	6.43	10.33	18.45	
70	7.72	11.60	23.20	
75	9.15			
77	9.96			
78.6	10.31			
<u>Phosphoric Acid</u>				
6	-0.90	0.63	0.64	0.998
10	-0.64	1.08	1.13	0.980
16	-0.33	1.78	1.94	0.963
20	-0.15	2.26	2.55	0.949
26	0.09	3.06	3.59	0.922
30	0.26	3.62	4.38	0.898
35	0.48	4.34	5.50	0.862
40	0.72	5.13	6.81	0.815
45	0.94	5.95	8.35	0.762
50	1.17	6.81	10.20	0.700
55	1.42	7.74	12.45	0.625
60	1.66	8.73	15.30	0.540
65	1.97	9.78	18.95	0.443
70	2.29	10.89	23.80	0.344
75	2.64	12.08	30.6	0.246
80	3.05	13.32	40.8	0.160
85	3.48	14.66	57.9	0.095

c. Some H₀ Data at 25°

Aqueous KOH and NaOH (35)			Methanolic NaOCH ₃ (38)		Ethanolic DMSO ^a (36)	
Molarity	H ₀		Molarity	H ₀	DMSO (mole %)	H ₀
	KOH	NaOH				
1	14.0	13.9	0.10	15.97	0	13.99
2	14.6	14.4	0.25	16.42	1	14.07
3	14.9	14.7	0.50	16.82	5	14.25
4	15.2	14.9	1.00	17.32	10	14.45
5	15.5	15.2	1.50	17.69	20	14.92
6	15.8	15.4	2.00	18.01	30	15.40
7	16.2	15.6	2.50	18.31	40	16.11
8	16.5	15.8			50	17.03
9	16.8	16.0			60	17.75
10	17.3	16.2			70	18.45
11	17.7	16.5			80	18.97
12	18.2	16.8			90	19.68
13		17.1			95	20.68
14		17.5				
15		17.8				
16		18.1				

^a10⁻²M in sodium ethoxide.

D. Properties of Commonly Used Strong Bases

The bases in this section have pK_a values (of the conjugate acid) generally above 15 and thus are classified as strong bases. More detailed information on any of these bases can be obtained from Fieser and Fieser, Reagents for Organic Synthesis, Vols. 1 and 2 (29) ; see also H. O. House, Modern Synthetic Reactions, W. A. Benjamin, New York, 1965, page 185. The references given are to the Fieser volumes (F for volume 1 and F2 for volume 2), and the comments are mostly paraphrases of their comments. These comments are not meant to limit possibilities of usage, but only to be interesting observations. Where a single use is noted, often the reagent can be used for many other types of reactions.

Refs.	Base	Formula	Mw	Solvents ^a	Comments	Ref.
70.	Choline	$[(CH_3)_3N^+CH_2CH_2OH]OH^-$	121.18	H ₂ O, MeOH	Similar to Triton B	F-142
79.	Claisen's alkali	CH ₃ OH-KOH	--	--	Extracts phenols insoluble in aqueous alkali	F-153
	Lithium amide	LiNH ₂	22.97	EtOH(s), λ-NH ₃ (s), PhCH ₃ (s)	Used for aldol condensations. Easier to handle than sodium amide	F-600
	Lithium diethylamide	LiN(C ₂ H ₅) ₂	79.07	HN(C ₂ H ₅) ₂ , DME, ether, THF	Used for opening epoxides	F-610 F2-247
	Lithium ethoxide	LiOC ₂ H ₅	52.00	EtOH	Generates carbenes from nitroso ureas; used in Wittig reactions	F-612
80	Lithium hydride	LiH	7.95	DME, ether(s)		F2-251
	Lithium nitride	Li ₃ N	34.83	Diox(s), diglyme(s)	Both solvents strongly enhance reactivity; converts acid chlorides to triamides	F-618 F2-251
	Naphthalene sodium	$[C_{10}H_8]^- Na^+$	151.16	DME, ether, THF	Better than sodium in THF for metalation of terminal acetylenes and active methylene compounds	F-711 F2-289
	Phenyl lithium	C ₆ H ₅ Li	84.04	Ether	Used in halogen lithium exchange reactions	F-845
	Phenyl potassium	C ₆ H ₅ K	116.20	Ether	Metalates active methylenes	F-848

Refs. p. 79.

Phenyl sodium	C_6H_5Na	100.10	Ether	Used in benzyne production	F-848
Potassium amide	KNH_2	55.13	ℓ - NH_3 , ether(s)	Flammable on contact with moisture; nitrates active methylene compounds in presence of alkyl nitrates; useful in dehydrohalogenations and Hoffmann degradations	F-907 F2-336
Potassium t-Butoxide	$(CH_3)_3COK$	112.21	t-BuOH, DME(s), DMF, DMSO, ether(s), PhH(s), Xy(s)	Good general base; probably most powerful alkoxide known	F-911 F2-336
Potassium ethoxide	KOC_2H_5	68.16	Ether(s), EtOH, PhCH ₃ (s)	Used as condensation catalyst	F-928
Potassium hydride	KH	40.11	Mineral oil suspension	More basic than sodium hydride	F-935 F2-346
Potassium hydroxide	KOH	56.10	EtOH, MeOH, H ₂ O	General base often used in ethanolic solution	F-935 F2-346
Potassium-2-methyl-2-butoxide	$\begin{array}{c} CH_3 \\ \\ CH_3CH_2C-OK \\ \\ CH_3 \end{array}$	126.24	t-AmylOH, ether, PhH, PhCH ₃	Good for formation of oximes with hindered acetophenones	F-939
Sodium amide	$NaNH_2$	39.02	DME(s), ether(s), ℓ - NH_3 (s), PhH(s), PhCH ₃ (s)	Good general base often used in dehydrohalogenations; once opened, it should all be used to prevent explosive decomposition products from forming	F-1034 F2-373
Sodium ethoxide	$NaOC_2H_5$	68.06	EtOH, ether(s)	General base often used in condensations and alkylations	F-1065

Refs.	Base	Formula	Mw	Solvents ^a	Comments	Ref.
p. 79.	Sodium hydride	NaH	24.01	DME(s), DMF(s), ether(s), PhH(s), PhCH ₃ (s), Xy(s)	Good for condensations and alkylations; forms benzyl tosylates from benzyl alcohols and tosyl chloride	F-1075 F2-382
	Sodium hydroxide	NaOH	40.00	H ₂ O	General base	F-1083
	Sodium methoxide	NaOCH ₃	54.03	DMF, DMSO, ether(s), MeOH, Pentane(s)	Yields dichlorocarbene from ethyl trichloroacetate; good general base	F-1091 F2-385
70	Sodium-2-methyl-2-butoxide	$\begin{array}{c} \text{CH}_3 \\ \\ \text{CH}_3\text{CH}_2-\text{C}-\text{ONa} \\ \\ \text{CH}_3 \end{array}$	94.14	t-AmyLOH, PhH, PhCH ₃ , Xy, ether	More soluble in organic solvents, especially aromatics, than t-butoxide	F-1096 F2-386
	Sodium methylsulfinylmethide (dimethyl sodium)	CH ₃ SOCH ₂ Na	100.11	DMSO (prepare Na salt from NaH and excess DMSO)	Often reagent of choice for Wittig reaction; several general and specific uses	F-310
	Tetraethylammonium hydroxide	(C ₂ H ₅) ₄ NOH ⁺	147.26			F-1138
	Triton B	C ₆ H ₅ CH ₂ N(CH ₃) ₃ OH	167.26	EtOH, MeOH, Py	Good condensation catalyst	F-1252
	Trityl lithium	(C ₆ H ₅) ₃ CLi	250.25	DME, ether, THF	Used to study compositions of enolate anions	F-1256 F2-454

Ref. 1	Trityl potassium	(C ₆ H ₅) ₃ CK	282.43	DME, ether(s), l-NH ₃	Useful in acyla- tions, alkylations, and carbonations	F-1258
29.	Trityl sodium	(C ₆ H ₅) ₃ CNa	266.32	DME, ether, PhH, PhCH ₃ , l-NH ₃	General condensa- tion catalyst	F-1259

^a The following shorthand for solvents is used: t-BuOH = t-butyl alcohol; Diox = dioxane; DME = 1,2-dimethoxyethane; DMF = dimethylformamide; DMSO = dimethylsulfoxide; ether = diethylether; EtOH = ethanol; Me₂CO = acetone; MeOH = methanol; l-NH₃ = liquid ammonia; PhCH₃ = toluene; PhH = benzene; py = pyridine; xy = xylene. A lowercase s in parentheses following the solvent indicates only slight solubility or suspension.

E. Standard Buffer Solutions

The data below provide information for the preparation of most standard and some special buffer solutions of specified pH values. More data are available in references 21 and 30.

1. Standard Buffer pH values^a

T (°C)	0.1M HCl	0.05M K- Tetraoxalate	Satd. (25°) Tartrate	KH- Phthalate	0.05M KH- Phthalate	Phosphate No. 1	Phosphate No. 2	0.01M Borax	Satd. (25°) Ca(OH) ₂
0	1.10	1.67		4.00		6.98	7.53	9.46	13.42
5	1.10	1.67		4.00		6.95	7.50	9.40	13.21
10	1.10	1.67		4.00		6.92	7.47	9.33	13.00
15	1.10	1.67		4.00		6.90	7.45	9.28	12.81
20	1.10	1.68	3.56	4.00		6.88	7.43	9.23	12.63
25	1.10	1.68	3.55	4.01		6.87	7.41	9.18	12.45
30	1.10	1.68	3.55	4.02		6.85	7.40	9.14	12.29
35	1.10	1.69	3.55	4.02		6.84	7.39	9.08	12.13
40	1.10	1.69	3.55	4.04		6.84	7.38	9.07	12.04
45	1.10	1.70	3.55	4.05		6.83	7.38	9.04	11.98
50	1.11	1.71	3.55	4.06		6.83	7.37	9.01	11.84
55	1.11	1.72	3.55	4.08		6.83	7.37	8.99	11.71
60	1.11	1.72	3.56	4.09		6.84		8.96	11.57

(Continued)

^aSolutions are prepared as follows:

0.1M hydrochloric acid. Dilute reagent grade HCl and titrate with standard base. Adjust to $0.1000 \pm 0.005M$.

Potassium tetraoxalate. Dissolve 1.271 g $KH_3(C_2O_4)_2 \cdot 2H_2O$ in water and dilute to 100 ml.

Potassium hydrogen tartrate. Allow salt to saturate in water at $25 \pm 3^\circ$.

Potassium hydrogen phthalate. Dissolve 1.021 g salt in water and dilute to 100 ml.

Phosphate No. 1. Dissolve 3.40 g (0.025m) KH_2PO_4 and 3.55 g (0.025m) anhydrous Na_2HPO_4 in water and dilute to 1 liter.

Phosphate No. 2. Dissolve 1.183 g (0.008695m) KH_2PO_4 and 4.320 g (0.03043m) Na_2HPO_4 in water and dilute to 1 liter.

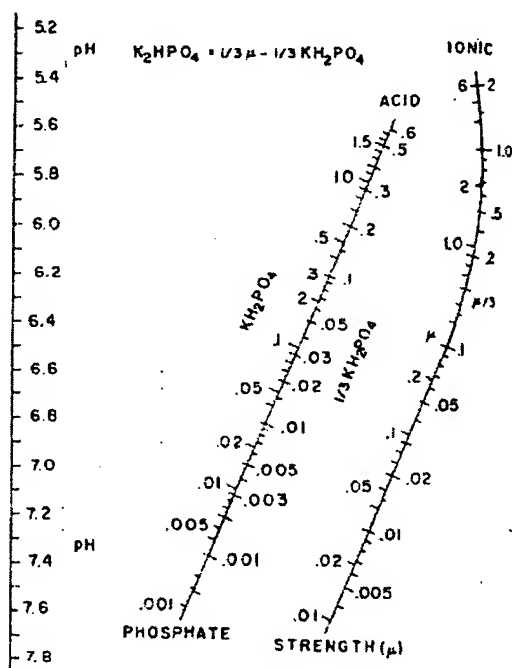
Borax. Dissolve 3.81 g of $Na_2B_4O_7 \cdot 10H_2O$ in water and dilute to 1 liter.

Calcium hydroxide. Allow reagent to saturate in water at 25° .

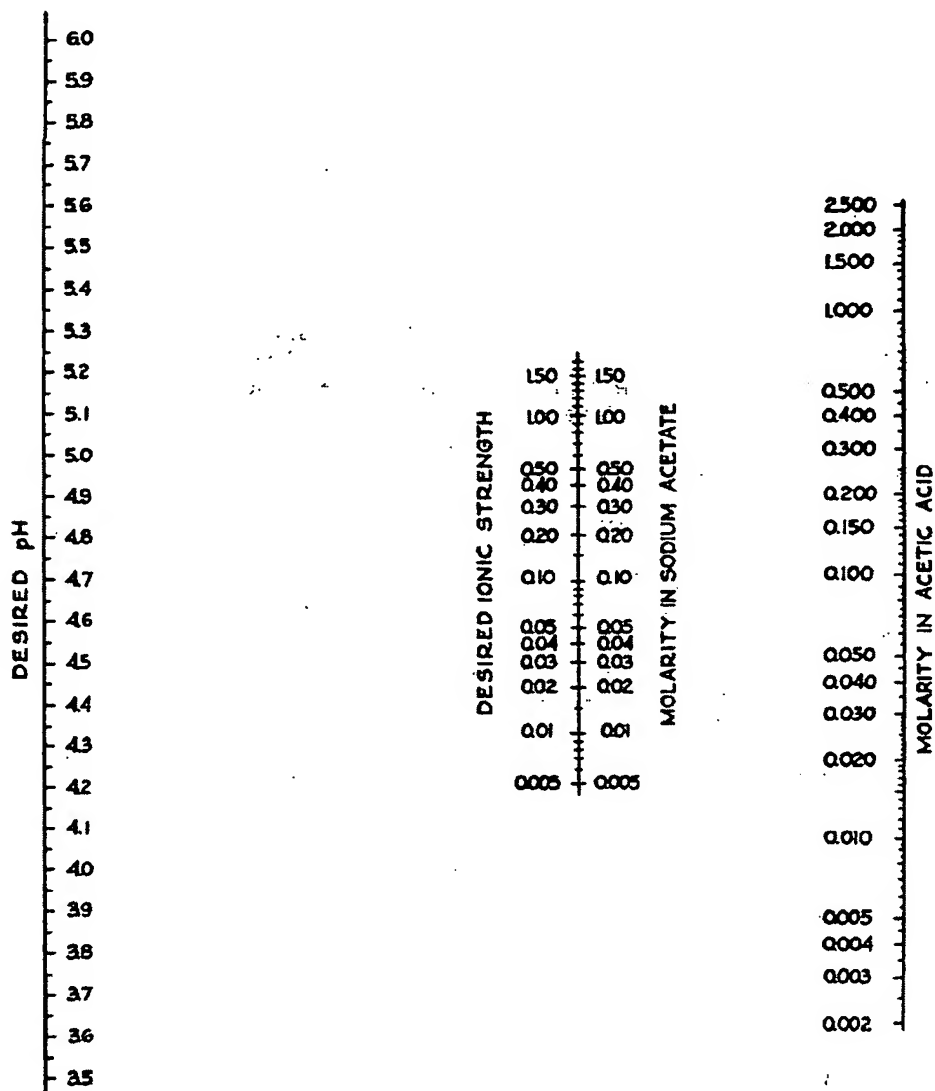
2. Nomograms for Acetate and Phosphate Buffers

The phosphate buffer nomogram below is used to determine the molar concentration of both KH_2PO_4 and K_2HPO_4 for the required solution. It is taken from W. C. Boyd, J. Biol. Chem., 240, 4097 (1965). For example, suppose a phosphate buffer of pH 7.4 and ionic strength 0.10 is desired. Position the straight edge between 7.4 on the pH scale, and 0.10 on the μ scale. Read 0.0096 on the KH_2PO_4 scale; then $[K_2HPO_4]$ is calculated using the equation shown at the top of the nomogram and the values read from the $1/3 KH_2PO_4$ and $\mu/3$ scales:

$$[K_2HPO_4] = 0.033 - 0.0033 = 0.0297M$$



The acetate buffer nomogram below is taken from W. C. Boyd, J. Amer. Chem. Soc., 67, 1035 (1945). For example, an acetate buffer of pH 4.8 and ionic strength 0.01 can be obtained with a solution 0.01M in sodium acetate and 0.0087M in acetic acid.



3. Miscellaneous Convenient Buffers

(a) Tris: made with HCl solutions of tris(hydroxymethyl)aminomethane (mw 121.14) and provide pH values from 7.55 to 9.67 (5°C), 7.00 to 9.10 (25°C), and 6.70 to 8.79 (37°C) depending on concentration. Sold as "Trizma" solutions or solid HCl salts by Sigma Chemical Co., 3500 DeKalb Street, St. Louis, Mo. 63118. For example, a 0.05M solution has pH values of 9.5, 8.9 and 8.6 at 5, 25, and 37°C, respectively.

(b) Succinate: a solution 0.05M in both NaHSuccinate and Na₂succinate has a pH of 5.34 (25°).

(c) Carbonate: a solution 0.05M in both NaHCO₃ and Na₂CO₃ has a pH of 9.93 (25°C).

(d) Na₃PO₄: a 0.05M Na₃PO₄ solution has a pH of 12.04 (25°C).

(e) Electrophoresis: see page 392 for electrophoresis buffers.

F. Primary Standards for Accurate Concentrations

A primary standard is a substance that can be used to make accurately known concentrations of active reagent. Often this solution is called the primary standard, while the substance used to make up the solution is called the primary standard substance. These substances must have a high degree of purity (>99.98%). The list below contains several substances that have been used as primary standards. The purity designation of these substances refers to the fact that Chem Sources, Directories Publishing Co., Flemington, N. J. lists them as being commercially available in very high purity (HP) or they are available from National Bureau of Standards as high purity reference substances (NBS) (see p. 496).

Constant-boiling hydrochloric acid has often been used as a primary standard; the concentration of HCl as a function of pressure is well known. A table showing this relationship appears below.

A secondary standard is one whose concentration (or purity) has been accurately determined by standardization with a primary standard. A sodium hydroxide solution for which the concentration had been accurately determined by titrating high purity benzoic acid is an example.

Name	Formula	Mw	Purity	Comment
Benzoic acid	C ₆ H ₅ CO ₂ H	122.123	NBS, HP	Dissolve about 0.5 g in about 50% ethanol and titrate using phenolphthalein as an indicator
Borax	Na ₂ B ₄ O ₇ · 10H ₂ O	381.360	NBS	Weak acid; dissolve in water and use methyl red as an indicator
Mercuric oxide	HgO	216.599	HP	Dissolve about 0.5 g with 15 g KBr in 25 ml water, excluding CO ₂ in the solution process. Use bromthymol blue as an indicator

Name	Formula	Mw	Purity	Comment
Potassium bicarbonate	KHCO_3	100.116		Use bromcresol green as an indicator; titrate to first tint of green
Potassium biiodate	$\text{KH}(\text{IO}_3)_2$	389.912		Strong acid; low solubility in water; use bromthymol blue as an indicator
Potassium biphthalate	$\text{KHC}_8\text{H}_4\text{O}_4$	204.224	NBS	Weak acid; use phenolphthalein as an indicator
Potassium bitartrate	$\text{KHC}_4\text{H}_4\text{O}_6$	188.178	NBS	Solution subject to molding, thus useful for only a few days; use phenolphthalein as an indicator
Sodium carbonate	Na_2CO_3	105.988	HP	Slightly hygroscopic and should be dried; titrate to first tint of green using bromcresol green

COMPOSITION OF CONSTANT-BOILING HCl (30)

Pressure (mm Hg)	Weight % HCl in Distillate	Weight of Distillate (g) Necessary to Make 1 Liter of 1 N HCl
770	20.197	180.407
760	20.221	180.193
750	20.245	179.979
740	20.269	179.766
730	20.293	179.555

Refs. 76.

G. Composition of Some Commercially Available Reagent-Grade Acids and Bases

These values, with the exception of the molecular weights, are approximate and are meant only to be representative of the reagents as commonly available in the United States. The more exact assay is usually printed on the bottle when purchased, but it should be kept in mind that concentrations change on exposure to air. This is particularly true for ammonium hydroxide. When making up a volumetric solution, therefore, it is better to use a little more than the calculated volume and then dilute if necessary. The millimeters of a concentrated reagent needed to make 1 liter of a solution of specified normality can be calculated with the formula:

$$V = \frac{100 \text{ MN}}{\text{bpd}}$$

where M is the molecular weight, N is the desired normality, b is the basicity ($\text{H}_2\text{SO}_4 = 2$, $\text{H}_3\text{PO}_4 = 3$, etc.), p is the percent acid (or base) in the concentrated reagent, and d is the specific gravity of that reagent. These data (p and d) are usually written on the reagent bottle.

Name	Formula	Mw	Normality of Conc. Reag.	% by Weight	Specific Gravity	Amount (ml) to Make 1 liter of 1N Solution
Acetic acid (glacial)	$\text{HC}_2\text{H}_3\text{O}_2$	60.052	17.4	99.8	1.05	57
Acetic acid (aqueous)			6.26	36	1.045	160
Ammonia	NH_3	17.031	14.8	29	0.90	65
Formic acid	HCO_2H	46.025	23.4	90	1.20	43
Hydriodic acid	HI	127.913	7.57	57	1.70	130
			5.51	47	1.50	180
Hydrobromic acid	HBr	80.912	8.90	48	1.50	120
Hydrochloric acid	HCl	36.461	12.0	37	1.19	83
Hydrofluoric acid	HF	20.006	28.9	49	1.16	35
Nitric acid	HNO_3	63.012	15.9	70	1.42	63
Perchloric acid	HClO_4	100.457	11.7	70	1.67	86
			9.5	60	1.54	110
Phosphoric acid	H_3PO_4	97.994	14.7	85	1.70	69
Potassium hydroxide	KOH	56.11	11.7	45	1.46	85
Sodium hydroxide	NaOH	40.00	19.1	50	1.53	52
Sulfuric acid	H_2SO_4	98.07	36	96	1.84	56
Sulfurous acid	H_2SO_3	82.09	0.7	6	1.02	-

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H. Approximate pH Values For Various Concentrations of Selected Substances

The approximate pH values are given here for a number of common substances at various concentrations.

Compound	1N	0.1N	0.01N	0.001N
Acetic acid	2.4	2.9	3.4	3.9
Ammonia	11.8	11.3	10.8	10.3
Benzoic acid			3.1	
Citric acid		2.1	2.6	
Hydrogen chloride	0.10	1.07	2.02	3.01
Hydrogen cyanide		5.1		
Potassium hydroxide	14.0	13.0	12.0	11.0
Sodium bicarbonate		8.4		
Sodium carbonate		11.5	11.0	
Sodium hydroxide	14.05	13.07	12.12	11.13
Sulfuric acid	0.3	1.2	2.1	

I. Acid-Base Indicators

The following common indicators cover the entire pH range (aqueous solutions). The data were taken from reference 30. For an extensive discussion of indicators for nonaqueous titrations, see reference 9.

Indicator	pH Range	Color		Preparation
		Acid	Base	
Methyl violet	0.1-1.5	Yellow	Blue	0.05% in water
Mentanil yellow	1.2-2.3	Red	Yellow	0.01% in water
Thymol blue (acid range)	1.2-2.8	Red	Yellow	0.1 g in 21.5 ml 0.01N NaOH + 229.5 ml water
Tropaeolin OO	1.4-2.6	Red	Yellow	1% in water
Methyl yellow	2.9-4.0	Red	Yellow	0.1% in 90% ethanol
Bromphenol blue	3.0-4.6	Yellow	Blue	0.1 g in 14.9 ml 0.01N NaOH + 235.1 ml water
Methyl orange	3.1-4.4	Red	Yellow	0.1% in water
Bromscresol green	3.8-5.4	Yellow	Blue	0.1 g in 14.3 ml 0.01N NaOH + 235.7 ml water
Methyl red	4.8-6.0	Red	Yellow	0.02 g in 60 ml ethanol + 40 ml water
Bromcresol purple	5.2-6.8	Yellow	Purple	0.02% in ethanol
Bromthymol blue	6.0-7.6	Yellow	Blue	0.1% in 50% ethanol
Phenol red	6.4-8.0	Yellow	Red	0.1% in ethanol
Neutral red	6.8-8.0	Red	Yellow	0.01 g in 50 ml ethanol + 50 ml water
Thymol blue (base range)	8.0-9.6	Yellow	Blue	0.1% in ethanol
Phenolphthalein	8.2-10.0	Colorless	Red	1% in ethanol
Thymolphthalein	9.4-10.6	Colorless	Blue	0.1% in ethanol
Alizarin yellow R	10.2-12.0	Yellow	Red	0.1% in water
Tropeolin O	11.0-13.0	Yellow	Orange	0.1% in water
Nitramine	10.8-13.0	Colorless	Brown	0.1% in 70% ethanol
1,3,5-Trinitrobenzene	11.5-14.0	Colorless	Orange	0.1% in ethanol

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